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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,435	DUNAYEVSKIY ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (e.g., see 7/1/04 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/04 has been entered. Claims 1-14, 21 and 22 were pending. Applicants amended claim 1. Therefore, claims 1-14, 21 and 22 are active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicants' amendments and/or arguments. The Nash et al. rejection under 35 U.S.C. § 102 is withdrawn in view of Applicants' amendment and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

3. Claims 1-14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaur et al. (Kaur, S.; McGuire, L.; Tang, D.; Dollinger, G.; Huebner, V. "Affinity Selection and

Mass Spectrometry-Based Strategies to Identify Lead Compounds in Combinatorial Libraries" *Journal of Protein Chemistry* **1997**, *16*, 5, 505-511) (**see IDS**) and Van Breemen et al. (Van Breemen, R. B.; Huang, C. –R.; Nikolic, D.; Woodbury, C. P.; Zhao, Y. –Z.; Venton, D. L. "Pulsed Ultrafiltration Mass Spectrometry: A New Method for Screening Combinatorial Libraries" *Anal. Chem.* **1997**, *69*, 2159-2164) (**of record**).

For ***claim 1***, Kaur et al. (see entire document) teach a method for identifying lead compounds in a combinatorial library wherein a target protein is mixed with a combinatorial library of potential ligands under conditions that allow for complex formation using hyphenated SEC-LC(reverse phase)-ESI technology (e.g., see Kaur et al., section 2.2; see also figure 1; see also first paragraph under Results and Discussion section). First, Kaur et al. disclose passing the reaction mixture through a first size-exclusion column to remove small molecular weight compounds that are less than a first preset value (see Kaur et al., paragraph bridging pages 506-507). Second, Kaur et al. disclose subjecting the size-excluded reaction mixture to conditions promoting dissociation of any ligand/target complex into free ligand and free target via a reverse-phase LC column (see Kaur et al., page 507, column 1, paragraph 1).

For ***claims 2-3***, Kaur et al. shows the separation of molecules that are in the range of 350-800 daltons (see Kaur et al., page 507, column 2, paragraph 1; see also figures 2a-c).

For ***claim 4***, Kaur et al. disclose a Pharmacia HR 10/10 size exclusion HPLC column (see Kaur et al., page 506, section 2.2).

For ***claim 5***, Kaur et al. disclose the use of 50/50/1 to 30/70/1 water/acetonitrile/acetic acid (see Kaur et al., page 506, column 2, paragraph 1).

For ***claims 13-14***, Kaur et al. disclose referencing the masses of the ligands identified with those predicted in the compound library (see Kaur et al., page 507, column 1, paragraph 1).

For ***claims 21-22***, Kaur et al. disclose the use of CID-MS/MS to confirm the identity and structure of any potential ligands (see Kaur et al., page 507, column 1, paragraph 1).

The prior art teachings of Kaur et al. differ from the claimed invention as follows:

For ***claims 1, 5-12***, Kaur et al. are deficient in that they do not teach the use of a second size exclusion medium. Kaur et al. only teach the use of a reverse-phase LC cartridge coupled to an electrospray mass spectrometer i.e., an LC-MS (note MS represents applicants elected method of detection i.e., mass spectrometry) step to dissociate the ligand/target complex instead of the required SEC-MS (see Kaur et al., page 507, column 1, paragraph 1).

However, Van Breemen et al. teach the following limitations that are deficient in Kaur et al.:

For ***claim 1 and 5-12***, Van Breemen et al. (see entire document) teach the use of a hyphenated ultrafiltration-mass spectrometry technique i.e., ultrafiltration-MS that can be used as a substitute for LC-MS (e.g., see Van Breemen et al., page 2160, column 1, last paragraph, "[a] liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the

HPLC column"). Furthermore, Van Breemen et al. disclose the use of organic solvents and acids to disrupt the protein-ligand complex (see Van Breemen et al., Experimental section; see also page 2163, column 2, paragraph 1). Van Breemen et al. also disclose the use of an ultrafiltration YM-10 (from Amicon) membrane and states that the cutoff of the membrane should be selected so as to retain the target protein i.e., if the protein is 40,000 than the cutoff must be less than 40,000 (e.g., a 10,000 molecular weight cutoff was used for the 41,250 MW adenosine deaminase target protein).

It would have been obvious to one skilled in the art at the time the invention was made to substitute the "ultrafiltration-MS" as taught by Van Breemen et al. for the "LC-MS" portion of the hyphenated SEC-LC-MS method as taught by Kaur et al. (i.e., a hyphenated SEC-ultrafiltration-MS method would result after substitution) because these two techniques are both used for the same purpose i.e., to elute bound ligands from a protein-ligand complex (e.g., compare Van Breemen, page 2161, figure 1, wherein bound ligands are "eluted" after dissociation from the ultrafiltration chamber, to Kaur et al., page 501, paragraph 1 wherein bound ligands are again "eluted" after dissociation from the reversed-phase cartridge). Furthermore, one of ordinary skill in the art would have been motivated to make such a substitution because Van Breemen et al. explicitly state that their ultrafiltration-MS method is better than LC-MS (e.g., see Van Breemen et al., page 2164, last paragraph, "Unlike these other mass spectrometry-base screening methods [i.e., referring to LC-MS, see previous sentence], pulsed ultrafiltration mass spectrometry allows the solution-phase receptor to be recovered or reused, which is a distinct advantage when the receptor protein is expensive or in short supply. In addition,

only pulsed ultrafiltration mass spectrometry allows library compounds to be extracted from a dilute solution and concentrated onto the receptor molecule, which overcomes common library solubility limitations"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Van Breemen et al. teach that LC-MS instrumentation can be readily adapted for ultrafiltration-MS (e.g., see Van Breemen, page 2161, column 1, paragraph 3, "A liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column [i.e., ultrafiltration-MS was substituted for LC-MS]").

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue **[1]** Kaur et al. fail to teach a second size exclusion column (e.g., see 3/2/04 Response, paragraph bridging pages 11-12), **[2]** Kaur et al. fail to teach "complex biological materials" because the materials "cannot be used in the method taught in Kaur et al. since it only allows binding of compounds with the highest affinities to bind to the receptor by using receptor-limiting incubation conditions" (e.g., see 3/2/04 Response, paragraph bridging pages 11-12). In addition, Applicants further state that the present method "requires a second

filtration step to remove large molecules under dissociating conditions specifically for the purpose of analyzing complex biological samples" (e.g., see 3/2/04 Response, bottom of page 11), **[3]** "Van Breemen et al. did not teach one to substitute ultrafiltration-MS technique for LC-MS technique; all that is implied is that an ultrafiltration chamber can be installed inside a liquid chromatograph instrument" (e.g., see 3/2/04 Response, paragraph bridging pages 11-12), **[4]** "Moreover, an ordinary skilled artisan would not find it obvious to even combine the teachings of both Kaur et al. and Van Breemen et al. ... both methods used in the cited publications would be similarly effective" (e.g., see 3/2/04 Response, paragraph bridging pages 13-14).

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Kaur et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the "combination" of references teach the second size exclusion column (e.g., see rejection above).

[2] First, the Examiner notes that it is not clear what Applicants mean by "receptor-limiting incubation conditions" and, as a result, Applicants' arguments are moot. Second, it should also be noted that in response to Applicants' argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "non" receptor-limiting incubation conditions and "large molecules") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants' implicitly argue that their claims are drawn

only to "non" receptor-limiting incubation conditions (otherwise their invention would not work, just as Applicants allege Kaur's invention does not work because they do not use "non" receptor-limiting incubation conditions i.e., the use receptor-limiting incubation conditions instead). However, Applicants' claims are not limited to these "workable" non-receptor limiting incubation conditions. In addition, Applicants' claims are not limited to complex biological materials that contain "large molecules". The pertinent parts of the specification cited by Applicants clearly show that "complex biological materials" can be "large" or "small" (e.g., see 3/2/04 Response, page 7, first full paragraph, "A sample of complex biological material .... span a wide range of molecular weights ... [and] may contain small inorganic or organic species ... **or** large macromolecular structures"). Please note that Applicants' "preset value" in claim 1 does not change this interpretation because the "preset value" could be a "small" number. Third, the combined teachings of Kaur et al. and Van Breemen et al. do provide samples that fall within Applicants' broad definition of "complex biological material" i.e., the samples fall within the "wide rand of molecular weights" and the samples represent "oligomeric biomolecules" (e.g., see 3/2/04 Response, page 7, first full paragraph wherein Applicants cite the pertinent parts of the specification that provide a definition for a "complex biological material").

[3] As an initial matter, the Examiner agrees with Applicants' assessment of the "instrument versus technique" misinterpretation in the recited passage (e.g., see 3/2/04 Response, page 12, middle paragraph, "[a] liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as a screening apparatus ... [etc]"). However, the Examiner does not agree that the ultrafiltration-MS could not be "substituted" for the LC-MS as outlined in the above rejection. To the contrary, a person of skill in the art would have been motivated to substitute

ultrafiltration-MS for LC-MS because both techniques are used for the same purpose (i.e., to dissociate a desired bound ligand from a ligand-target complex) and ultrafiltration-MS provides several advantages including the ability to recover potentially expensive solution-phase receptors and also further allows for the extraction of dilute solutions of library members that would avoid potential solubility problems (e.g., see newly amended rejection above).

[4] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Examiner respectfully disagrees with Applicants' statement that the "cited publications would be similarly effective" (e.g., see 3/2/04 Response, page 13, last paragraph). To the contrary, van Breemen et al. explicitly state that ultrafilitration-MS is better than LC-MS because the potentially expensive "solution-phase receptor" can be recovered (e.g., see van Breemen et al., page 2164, last paragraph). In addition, van Breemen et al. also state, "In addition, only pulsed ultrafilitration mass spectrometry allows library compounds to be extracted from a dilute solution and concentrated onto the receptor molecule, which overcomes common library solubility limitations (e.g., see van Breemen et al., page 2164, last paragraph). Thus, it is clear that the two cited publication would NOT be similarly effective. Thus, ample motivation to combine said references has been provided. Please also note that "there is no requirement that

the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-5, 13, 14, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jindal et al. (WO 97/01755) (Date of Patent is **16 January 1997**).

For ***claims 1, 4***, Jindal et al. (see entire document) disclose methods for screening a sample including target/ligand complexes using "multi-dimensional" column chromatography techniques (e.g., see Jindal et al., abstract), which anticipates claim 1. For example, Jindal et al. disclose **[1-2]** mixing a protein target and a sample of complex biological material in solution to form a reaction mixture and incubating the reaction mixture under conditions allowing complex formation by the target and any target-binding ligand present in the sample (e.g., see page 5, lines 14-20, "the claimed multi-dimensional methods involve combining [i.e., mixing] a solution of heterogeneous

ligands [i.e., the complex biological material] with the target of interest [i.e., the protein] to screen the ligands on the basis of one or more binding characteristics. Ligands ... bind to the target of interest to form a target/ligand complex"; see also Field of the Invention, "More specifically, the invention is directed toward ... hi-flux screening of natural and synthetic libraries"; see also paragraph bridging pages 13-14, "Natural libraries may be ... a solution as found in nature without prior manipulation"; see also page 2, first full paragraph). In addition, Jindal et al. disclose **[3]** passing the reaction mixture through a first size-exclusion (SEC) medium that removes from the reaction mixture any small molecular weight compounds each having a molecular weight less than a first preset value (e.g., see page 5, lines 20-22, "The complex [i.e., the first preset value] then optionally is separated from the unbound components using any of a variety of separation techniques, e.g., size exclusion."; see also page 31, last paragraph, "When one introduces this mixture to an SEC system, unbound components will diffuse into the pores of the SEC matrix, however the complex, and the target are excluded because of their size. Because the macromolecular target/ligand complex moves through an SEC column faster than the lower molecular weight components, the complex will elute from the column first. The eluate containing target/ligand complexes can then be introduced to a second dimension [i.e., the unbound ligands are excluded]"). Jindal et al. also disclose **[4]** subjecting the size-excluded reaction mixture from step (3) to conditions promoting dissociation of any ligand/target complex into free ligand and free target (e.g., see page 15, lines 15-19, "Selection of peptides based on their binding constant can be achieved ... [via] a chromatographic system in which the components of the RL complex are

separated as the complex dissociates"; see also page 17, line 13, "Free ligand is swept from the system before it has the chance to re-complex with R to form RL"; see also page 15, lines 20-25, "The methods described herein allow us to select on the basis of the forward rate constant of a ligand for the receptor, the reverse (off) rate constant, or the equilibrium constant under conditions where it is possible to vary ionic strength, pH, concentration of competitive binding agents, organic solvent concentration, and temperature"). Finally, Jindal et al. disclose **[5]** passing the reaction mixture resulting from step (4) through a second size exclusion medium that removes from the reaction mixture any molecule larger than a second present value (e.g., see page 23, last paragraph, "The methods of the invention use a tandem column chromatographic technique: ... the columns in the system may be chosen from ... size exclusion columns ... the columns are arranged so that the eluate of one column [i.e., the first column] is directly introduced into the second column"; see also page 31, lines 10-11, "The first dimension [i.e., first column] ... [is] a size exclusion chromatography system ... capable of separating target/ligand complexes and unbound components"; see also page 32, first full paragraph, "The second column may be a size exclusion column. The eluted target/ligand complexes from the first column are then introduced to the second column, along with a known ligand. The known ligand can be any ligand known to bind at the particular epitope one is seeking a binder to. Thus, the known ligand will compete with the ligand on the target/ligand complex, and displace ligands which bind at the selected site on the target molecule"; see also age 31, last paragraph; see also claim 12). Thus, Jindal et al. envisions many column chromatographic systems including an SEC-SEC

tandem configuration for monitoring protein-ligand interactions (Please note that other configurations like SEC-affinity-SEC disclosed by Jindal et al. would also anticipate the claims).

For ***claims 2-3***, Jindal et al. do not disclose a specific molecular weight cutoff (e.g., 2000 or 1,500 daltons) for the molecular weight ligands, however, they do define a ligand as a "generic term referring to the structurally distinct chemical species that are dissolved in a solvent and constitute a library", which would encompass small molecular weight compounds and provide several examples of ligands in the examples that are less than 2000 or 1,500 daltons (e.g., see Example 2F wherein a XXXXX library was produced wherein X represent any one of the 20 naturally occurring amino acids i.e., GGGGG ~ 303 mw << 1,500 daltons). In addition, Jindal et al. state that their ligands can be "small" in size (e.g., see page 22, line 14). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 5***, Jindal et al. disclose the use of an organic solvent (e.g., see page 15, line 23).

For ***claim 13-14***, Jindal et al. disclose the use of various "reference standards" (e.g., see page 41, last paragraph).

For ***claims 21-22***, Jindal et al. disclose, for example, analysis via mass spectrometry (e.g., see Jindal et al., claim 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-14, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (WO 97/01755) (Date of Patent is **16 January 1997**) and Van Breemen et al. (van Breemen, R. B.; Huang, C. –R.; Nikolic, D.; Woodbury, C. P.; Zhao, Y. –Z.; Venton, D. L. "Pulsed Ultrafiltration Mass Spectrometry: A New Method for Screening Combinatorial Libraries" *Anal. Chem.* **1997**, *69*, 2159-2164) (**of record**).

For ***claims 1-5, 13, 14, 21 and 22***, Jindal et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-5, 13, 14, 21, 22 and, consequently, also renders obvious claims 1-5, 13, 14, 21 and 22.

The prior art teaching of Jindal et al. differs from the claimed invention as follows:

For ***claims 6***, Jindal et al. are deficient in that they do not teach the use of ultrafiltration.

For ***claims 7-12***, Jindal et al. are deficient in that they do not teach the use of MS <2000 daltons.

However, Van Breemen et al. teach the following limitations that are deficient in Jindal et al.:

For ***claim 6***, Van Breemen et al. (see entire document) teach the use of a hyphenated ultrafiltration-mass spectrometry technique i.e., ultrafiltration-MS that can be used as a substitute for LC-MS (e.g., see Van Breemen et al., page 2160, column 1, last paragraph, "[a] liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column"). Furthermore, Van Breemen et al. disclose the use of organic solvents and acids to disrupt the protein-ligand complex (see Van Breemen et al., Experimental section; see also page 2163, column 2, paragraph 1).

For ***claim 7-12***, Van Breemen et al. also disclose the use of an ultrafiltration YM-10 (from Amicon) (e.g., a 10,000 molecular weight cutoff was used for the 41,250 MW

adenosine deaminase target protein). Ultrafiltration are also commercially available in smaller sizes including YM-3 (i.e., 3,000 dalton cutoff) and YM-2 (i.e., 2,000 dalton cutoff).

It would have been obvious to one skilled in the art at the time the invention was made to substitute the "ultrafiltration-MS" as taught by Van Breemen et al. for the "LC-MS" portion of the hyphenated SEC-LC-MS embodiments as taught by Jindal et al. (i.e., a hyphenated SEC-ultrafiltration-MS method would result after substitution) because these two techniques are both used for the same purpose i.e., to elute bound ligands from a protein-ligand complex (e.g., compare Van Breemen, page 2161, figure 1, wherein bound ligands are "eluted" after dissociation from the ultrafiltration chamber, to Jindal et al., page 32, first full paragraph, "The second column may be a size exclusion column. The eluted target/ligand complexes from the first column are then introduced to the second column, along with a known ligand. The known ligand can be any ligand known to bind at the particular epitope one is seeking a binder to. Thus, the known ligand will compete with the ligand on the target/ligand complex, and displace ligands which bind at the selected site on the target molecule"). Furthermore, one of ordinary skill in the art would have been motivated to make such a substitution because Van Breemen et al. explicitly state that their ultrafiltration-MS method is better than LC-MS (e.g., see Van Breemen et al., page 2164, last paragraph, "Unlike these other mass spectrometry-base screening methods [i.e., referring to LC-MS, see previous sentence], pulsed ultrafiltration mass spectrometry allows the solution-phase receptor to be recovered or reused, which is a distinct advantage when the receptor protein is expensive or in short supply. In

addition, only pulsed ultrafiltration mass spectrometry allows library compounds to be extracted from a dilute solution and concentrated onto the receptor molecule, which overcomes common library solubility limitations"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Van Breemen et al. teach that LC-MS instrumentation can be readily adapted for ultrafiltration-MS (e.g., see Van Breemen, page 2161, column 1, paragraph 3, "A liquid chromatograph-electrospray mass spectrometer (LC-MS) was used as the screening apparatus, except that an ultrafiltration chamber was substituted for the HPLC column [i.e., ultrafiltration-MS was substituted for LC-MS]").

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 10, 2004

BENNETT CELSA
PRIMARY